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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,939	11/04/2003	David J. Ecker	ISIS-5318	5964

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EXAMINER

WOLLENBERGER, LOUIS V

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/700,939

Applicant(s)

ECKER ET AL.

Examiner

Louis V. Wollenberger

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-83 is/are pending in the application.
- 4a) Of the above claim(s) 2-23, 25-35 and 37-83 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 24 and 36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: See Continuation Sheet.

Continuation of Attachment(s) 6). Other: IDS statements: 1/5/04, 5/13/04, 4-26-2004, 8-12-2004, 9-13-2004, 1/18/05, 1-28-2005, 3-14-2005, 3-21-2005, 4-05-2005, 4-21-2005, .

DETAILED ACTION

Election/Restrictions

Applicants' timely election without traverse of Group IX, Claims 1, 24, and 36 in the reply filed on 6/16/2006 is acknowledged.

Status of the application

Claims 1–83 are pending. Claims 2-23, 25-35, and 37-83 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 24, and 36 are examined herein.

Priority

Applicant's claim for continuing application priority under 35 USC §120 and provisional application priority under 35 USC §119(e) are acknowledged. However, U.S. Non-Provisional Applications 10/078,949, 09/479,783, 08/870,608, 08/659,440 and U.S. Provisional Application 60/423,760 fail to provide adequate support under 35 USC §112 for Claims 1, 24, and 36 of this application.

In the instant case, no support was found in the U.S. Provisional and Non-Provisional Applications listed for claims drawn to compositions comprising first and second oligomers, having complementarity to one another and to a selected target, and wherein at least one of the oligomers has a non-linear secondary structure or is part of a multiple oligomer assembly.

Additionally, no support could be found in the instant applications for claims to polynucleotide matrices comprising a plurality of polynucleotide monomers, wherein each monomer has an intermediate region comprising a linear double stranded waist region, as recited in claim 24.

If applicant believes that support for claims 1, 24, and 36 is present in the earlier filed priority documents, applicant must, in responding to this Office Action, point out with particularity, where such support may be found.

For purposes of this examination, the effective filing date of claims 1, 24, and 36 is that of US Application 10/660,059, filed 9/11/2003, now abandoned.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;

- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Claim 36 is drawn to a pharmaceutical composition comprising the oligomeric assembly of claim 1 and a pharmaceutically acceptable carrier.

The “pharmaceutical composition” and “pharmaceutically acceptable carrier” language in combination with the fact that the specification (page 8 and pp. 76-78) discloses using the oligomeric compositions for treating or preventing a disease or condition, wherein the methods comprise administering such oligomeric assemblies to a patient having or predisposed to the disease or condition, requires that these claims be evaluated to determine whether the specification teaches how to use these compositions for treating these conditions.

Problems related to the pharmaceutical use of antisense nucleic acids are well known in the art. Such problems include the inability to routinely deliver an effective concentration of a specific nucleic acid in a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Jen et al. (2000) *Stem Cells* 18:307-319 teach that

"One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive." (page 313, second column, second paragraph):

Opalinska et al. (2002) *Nature Reviews* 1 :503-514 teach that

“[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA” and in column 2 of the same page, “Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded.” (page 511)

Given this unpredictability, the skilled artisan would require specific guidance to practice use the claimed pharmaceutical compositions to treat or prevent one or more disorders *in vivo* in any given patient. That is, specific guidance would be required to teach one of skill in the art how to use the claimed compositions to produce a positive effect in a patient.

A review of the instant application fails to find exemplary disclosure illustrating the proposed use of the compositions to treat any organism, mammal, or human subject. Instead, the specification makes general assertions that one of skill in the art would know how to administer (dose, frequency, and duration) the claimed oligomeric assemblies (pages 76-83). Examples of *in vivo* use of the pharmaceutical compositions, working or otherwise, are not provided. Moreover, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery to a cultured cell would not be applicable to delivery of oligonucleotides to any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of the claimed pharmaceutical compositions *in vivo* by the broadly disclosed methodologies of

the instant invention, would result in the assemblies reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed pharmaceutical compositions in the manner disclosed to produce the intended effects of treating the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the “pharmaceutical” language from the instant claims would overcome this rejection, but may trigger a separate rejection under either 35 USC §102 or §103, in view of the prior art cited below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 24, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Cantor et al. (US Patent 5,561,043).

Cantor et al. teach a multimeric nucleic acid construct comprising a plurality of single stranded nucleic acid molecules, or species (Fig. 1A-B). It is taught that antibody and oligonucleotide specificities are combined to greatly amplify the accumulation of functional moieties at the site or sites of a disorder in vivo or the detection of a disorder or other contaminant in vivo or in vitro (column 3, lines 30-40). It is taught that the presence of the nucleic acids allows for hybridization between complementary bases which further increases binding affinity and specificity between complementary sequences in natural settings (column 3, lines 45-60).

The nucleic acid molecules are interlinked via hybridization through complementary base pairing. The nucleic acid molecules may be further linked to a streptavidin molecule, which, in turn, may be bound to a biotinylated antibody. Cantor et al. further teach that the streptavidin/biotin linked nucleic acid multimer may be further attached to functional groups, as illustrated in Fig. 1B (column 3, lines 60-67). According to Cantor et al., functional groups may include genes and/or other nucleic acids (columns 4, lines 1-5; column 6, lines 45-50). Cantor et al. further teach that a part or portion of the nucleic acid species may itself be the functional

group (column 4, lines 25-30). For example, a nucleic acid sequence can be engineered into the species to be bound to streptavidin and the resulting construct utilized (column 4, lines 25-35).

The constructs are said to be useful for the treatment or diagnosis of disorders *in vitro* or *in vivo*, and for the detection of target substances (column 1, lines 15-25). For instance, Canter et al. specifically recognize that oligonucleotides may be used as antisense molecules to inhibit gene expression (column 1, lines 25-30). It is said that the nucleic acid species of the multimeric complex may be DNA or RNA (column 4, lines 45-46).

Cantor et al. teach that the sequence of each of the nucleic acid species, including the first, second, third, or more species may be the same or different, may comprise a small or large number of complementary sequences, and may have a defined or random sequence (column 5, lines 17-21). It is specifically stated that nucleic acids may be complementary providing a further binding function to each construct (column 5, 29-32). For instance, it is stated that, with regard to the nucleic acid molecules, specific nucleotide sequences may be engineered into one or more of the nucleic acid species to attract a particular pharmaceutically active component (column 6, lines 35-45). Canter et al. teach that the invention may be used for *in vitro* detection of a target (column 8, lines 9-15). Targets may include nucleic acids (column 8, lines 26-28; column 9, lines 1-5).

At column 11, Example 2, lines 49-55, Canter et al. explicitly teach that dendrimeric nucleic acid complexes may include synthetic Holiday junctions with pendant single stranded ends. Accordingly, this embodiment appears to teach a structure within the scope of claim 24.

Also disclosed are pharmaceutical compositions thereof for use as an *in vitro* and *in vivo* diagnostic and/or therapeutic reagent (column 5, lines 38-45).

Thus, Cantor et al. anticipates the instant claims.

Claims 1, 24, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Hogan et al. (US Patent 5,424,413).

Hogan et al. teach a branched nucleic acid structure comprising at least one nucleic acid strand comprising at least two separate target regions, which may be on the same or different molecules, and two distinct arm regions, wherein the two separate target regions hybridize to a target nucleic acid, and wherein the two distinct arm regions do not hybridize with the target nucleic acid but possess complementary regions that are capable of hybridizing with one another (Fig. 1; column 1, lines 50-60).

It is said that the invention may be used as a probe to detect the presence and amount of a target nucleic acid (column 1, lines 67-68 to column 2, line 1). It is also taught that the probes may be used in a variety of therapeutic applications, necessitating the use of pharmaceutically acceptable carriers (column 25, lines 25-34). It is further taught that the branched complex may form a 3-way junction or may have up to 5 or 10 junctions (column 25, lines 1-10).

Thus, Hogan et al. anticipates the instant claims.

Claims 1 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Nilsen (US Patent 6,274,723).

Nilsen teaches a dendritic polynucleotide having a plurality of single stranded hybridization arms; said polynucleotide comprising a plurality of polynucleotide monomers bonded together by hybridization; each polynucleotide monomer having an intermediate region comprising a linear, double stranded waist region having a first end and a second end, said first end terminating with two single stranded hybridization regions, each from one strand of the waist region, and said second end terminating with one or two single stranded hybridization regions, each from one strand of the waist region; and in said dendritic polynucleotide each polynucleotide monomer is hybridization bonded to at least one other polynucleotide monomer and at least one such hybridization region (column 2, lines 43-60). The dendritic nucleic acids are said to be useful for the development of nucleic acid diagnostics as signal amplification tools (column 2, top). They are also said to have potential as drug (antisense) delivery vehicles (column 2, top).

Claim 6 of US Patent 6,274,723 specifically claims a composition for use as a hybridization reagent for detection of a nucleic acid sequence, comprising a polynucleotide matrix having a plurality of single stranded hybridization arms; said polynucleotide matrix comprising a plurality of polynucleotide monomers bonded together by hybridization; each polynucleotide monomer having an intermediate region comprising a linear, double stranded waist region having a first end and a second end, said first end terminating with two single stranded hybridization regions, each from one strand of the waist region, and said second end terminating with one or two single stranded hybridization regions, each from one strand of the waist region; and in said polynucleotide matrix each polynucleotide monomer is hybridization bonded to at least one other polynucleotide monomer at at least one such hybridization region;

and wherein each of said hybridization regions and said waist regions of said plurality of monomers comprise sequences obtained from a master sequence containing no repeats of subsequences having X nucleotides, wherein X represents an integer of from 2 to 6.

Furthermore, page 48 of the instant application specifically teaches that US Patent 6,274,723 describes a dendritic polynucleotide within the scope of the instant invention.

Thus, Nilsen anticipates the instant claims.

Claims 1, 24, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Porta and Lizardi (1994) *Biotechnology* 13:161-164.

Porta et al. teach an allosteric, hammerhead ribozyme that is sensitive to the presence of a DNA oligonucleotide effector molecule. The ribozyme comprises a loop domain having a sequence complementary to the effector and a catalytic domain having a sequence complementary to a specific nucleic acid target-in this case a radioactively labeled, synthetic 38-nt RNA (Fig. 1). The catalytic activity of the ribozyme is dependent on the presence or absence of the effector. When the effector is present, it hybridizes to the ribozyme, inducing a catalytically favorable conformational change, and thereby enhancing the rate of ribozyme-catalyzed cleavage of the 38-mer target RNA. A 12-nucleotide facilitator oligonucleotide, complementary to the 5'-end of the substrate may also be used to improve catalytic efficiency.

Porta et al. teach a solution-phase assay, wherein the rate of the ribozyme catalyzed reaction (i.e., target nucleic acid cleavage) is measured by polyacrylamide gel electrophoresis;

the relative amounts of the fragments formed over time indicates the rate of catalysis (Fig. 2). Porta et al. teach that the extent of cleavage of the target nucleic acid, expressed as a percentage of a control, varies significantly, depending on whether the correct effector is present or absent. In the absence of the correct effector sequence, and in the presence of an unrelated (e.g., M13) ssDNA effector, only 5% cleavage is measured (page 161 and see Fig. 2); in the presence of an imperfect effector molecule, only 18%; and in the presence of the correct effector, 53%-78%. The relative extent of cleavage, and therefore the relative activities of the ribozyme under different conditions, is readily evaluated by measuring the relative radioactivities of the cleavage bands following gel electrophoresis.

Thus, Porta et al. describe a method for detecting the presence or absence of a specific nucleic acid sequence (the effector) by measuring the relative rate of a chemical reaction catalyzed by an allosteric ribozyme—a nucleic acid sensor—towards a specific target nucleic acid, the reporter.

Accordingly, Porta et al. teach a multiple oligomer assembly, as recited by claim 1, comprising a plurality of polynucleotide monomers, as recited by claim 24, which in this case correspond to a ribozyme having self-complementary and target complementary regions, a substrate or target nucleic acid, an effector, and a facilitator (Fig. 1B). At page 162, 2nd column, bottom, Porta et al. teach that allosteric ribozymes in general are useful for the *in vivo* cleavage of an mRNA target in response to the presence of a specific inducer (effector) sequence that is only found in a specific cell type. Accordingly, one of skill in the art would recognize the necessity for formulating a ribozyme for such use in a pharmaceutically acceptable carrier.

Thus, Porta et al. anticipate the instant claims.

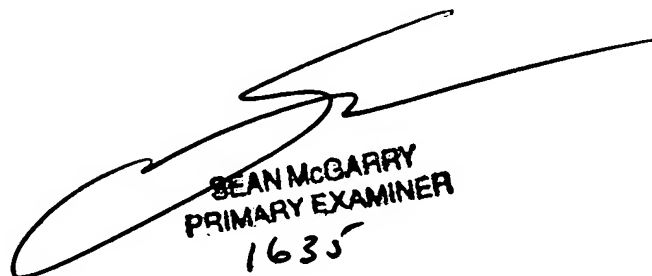
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis Wollenberger
Examiner, Art Unit 1635
July 6, 2006


SEAN MCGARRY
PRIMARY EXAMINER
1635